SYNOPSIS

Issue Date: 19 June 2012

Name of Sponsor/Company	Janssen-Cilag N.V./S.A.
Name of Finished Product	Invega®
Name of Active Ingredient(s)	Paliperidone ER

Protocol No.: R076477SCH3038

Title of Study: Open-label, single arm, interventional study to explore the efficacy and safety of paliperidone ER in the management of patients with acute agitation and/or aggression

Study Name: IMPACT (**I**nvega in the **M**anagement of **P**atients in the **AC**ute setting)

EudraCT Number: 2009-015629-35

Coordinating Investigator(s): [redacted], MD

Study Center(s): 19

Publication (Reference): None at the time of reporting

Study Period: 28 March 2010 – 19 December 2011

Phase of Development: 4

Objectives:

PRIMARY

The primary objective of this study was to evaluate the efficacy and safety during first days of treatment with paliperidone extended release (ER) in subjects with acute agitation and/or aggression in the context of psychosis in the psychiatric emergency setting. The primary endpoint was the number of subjects having an improvement of 40% or more on Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC) (= response) at Day 6 or early termination compared to baseline.

SECONDARY

The secondary objective of this study was to explore the efficacy, tolerability and safety of the use of paliperidone ER in subjects presenting with symptoms of agitation and/or aggression in the context of psychosis.

This was done by:

- assessing the change from baseline on the PANSS-EC; evaluation was done after 2 hours and after 6 to 12 hours. Data were also collected on Days 2, 3, 4, 5 and 6.
- assessing the change from baseline on the OAS (Overt Aggression Scale); evaluation was done after 2 hours and after 6 to 12 hours. Data were also collected on Days 2, 3, 4, 5 and 6.
- assessing the change from baseline on disease severity (Global Assessment of Functioning [GAF]); evaluation was done after 6 to 12 hours. Data were collected on Days 2, 3, 4, 5 and 6.
- differentiate between extreme agitation and extreme sedation (Behavioural Activity Rating Scale [BARS], a 7-point categorical evaluation scale); evaluation was done at baseline, after 2 hours and after 6 to 12 hours. Data were also collected on Days 2, 3, 4, 5 and 6.
- assessing tolerability and safety by reporting adverse events (AEs) and vital signs. Evaluation was done at baseline, after 2 hours and after 6 to 12 hours. Data were also collected on Days 2, 3, 4, 5 and 6.
- assessing the use of lorazepam.
- the most likely psychiatric diagnosis, based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria, was collected at end of study.

Methodology:

This was an open-label, single arm, multicenter 6-day study to explore efficacy, tolerability and safety of paliperidone ER in subjects with symptoms of agitation and/or aggression in the context of psychosis, presenting at the emergency ward.

Approximately 75 subjects, coming from 15-20 centers were planned to participate in this study. The planned number of subjects per investigational site was 5, with a maximum of 15 subjects.

The study consisted of a screening visit, a 5-day treatment period with paliperidone ER, and a final visit. The study ended after 5 days of treatment or at the day of discharge from the hospital, whichever came first.

Throughout the study, dosing of 6 or 9 mg/day could be used. In general, the recommended paliperidone ER dose was 6 mg once daily. For subjects with an acute exacerbation of schizophrenia in a real-world setting, an initial dose of paliperidone ER 9 mg once daily was also assumed to provide optimal clinical efficacy with good tolerability. Lorazepam could be administered according the investigators' discretion up to a maximum of 7.5 mg/day.

Other psychotropics were not allowed during this study. However, the continuous long-term use of mood stabilizers and/or anti-depressants in a stable dosage, started at least 72 hours prior to enrollment, was allowed. Biperidene (up to 4 mg/day) or trihexyphenidyl (up to 10 mg/day) or other available anticholinergics could be used for the treatment of extrapyramidal symptoms (EPS). The investigator had to reevaluate the need for anticholinergic medication on an ongoing basis. The sponsor had to be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies were administered.

Efficacy was evaluated by means of PANSS-EC, OAS, GAF, BARS, and the use of lorazepam. Safety assessment was based on reported AEs and vital signs measurements.

Number of Subjects (planned and analyzed): Approximately 75 subjects, coming from 15-20 centers were planned to participate in this study. In practice, 56 subjects were included and treated in this study.

Diagnosis and Main Criteria for Inclusion: Adult male and female subjects (≥ 18 years) who were presenting with acute agitation and/or aggression in the context of psychosis, suspected schizophrenia and who had a PANSS-EC score of 20 or above were eligible for this study. Subjects were outpatients in need of hospitalization, according to physician's discretion. Female subjects of childbearing potential needed to have a negative pregnancy test at baseline and further adequate anticonceptive protection.

Subjects who received benzodiazepines 4 hours prior to enrollment or antipsychotics 72 hours prior to enrollment as well as subjects who received clozapine or a long-acting injectable antipsychotic drug during the last 3 months were excluded. In addition, subjects presenting with agitation, aggression or violent behavior that necessitated the use of intramuscular or intravenous medication were excluded. Female subjects may not have been pregnant or breast-feeding.

Test Product, Dose and Mode of Administration, Batch No: paliperidone ER at 2 dosage levels (6 and 9 mg/day). In general, the recommended paliperidone ER dose was 6 mg once a day. For subjects with an acute exacerbation of schizophrenia in a real-world setting an initial dose of paliperidone 9 mg once daily was also assumed to provide optimal clinical efficacy with good tolerability. The subject was instructed to always take paliperidone ER in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state (batch numbers: paliperidone-ER 6-mg tablet: 361885, 363140, and 364469; paliperidone-ER 9-mg tablet: 361886, 363141, and 364522).

A benzodiazepine (i.e., lorazepam 2.5 mg) for sedation and/or rescue medication could be added with a maximum of 7.5 mg/day, at the investigators' discretion (batch numbers lorazepam: 361884 and 363142).

Duration of Treatment: 5 days

Criteria for Evaluation:

EFFICACY EVALUATIONS/CRITERIA:

All subjects who received at least 1 dose of study medication (i.e., intent-to-treat [ITT] population) were included in efficacy data analyses.

For all efficacy parameters, the changes at the end of the study (Day 6 or last postbaseline visit) compared to baseline were used to characterize the treatment response in all subjects.

Efficacy parameters included the following:

- PANSS-EC
- OAS
- BARS
- patient's global functioning, assessed using the GAF scale
- the use of lorazepam was recorded at each time point
- the most likely psychiatric diagnosis based on DSM-IV was recorded at endpoint.

SAFETY EVALUATIONS:

Adverse Events: AEs were reported by the subject for the duration of the study.

Vital Signs: Systolic and diastolic blood pressure (SBP, DBP) and pulse rate were recorded at each visit throughout the study.

Statistical Methods: Descriptive statistics, intent-to-treat analysis, frequency distributions.

RESULTS:

STUDY POPULATION:

The study included 56 subjects who were treated with 6 or 9 mg paliperidone ER once daily. Overall, 45 out of 56 subjects (80.4%) completed the study. Eleven subjects (19.6%) discontinued the study prematurely. The main reason for study discontinuation was recovery of symptoms (3 subjects, 5.4%).

Subject Disposition and Completion/Withdrawal Information
(R076477SCH3038 Study: ITT Analysis Set)

	Treatment Paliperidone ER				
	Paliperidone ER 6 mg only	Paliperidone ER 9 mg only	Paliperidone ER switch 0 to 6 mg	Paliperidone ER switch 6 to 9 mg	Total
Screened, N	-	-	-	-	56
Treated, N	35	15	4	2	56
Completed, n (%)	28 (80.0)	14 (93.3)	1 (25.0)	2 (100.0)	45 (80.4)
Discontinued, n (%)	7 (20.0)	1 (6.7)	3 (75.0)	0	11 (19.6)
Recovery of the symptoms[a]	3 (8.6)	0	0	0	3 (5.4)
Lack of efficacy	1 (2.9)	0	0	0	1 (1.8)
Other	3 (8.6)	1 (6.7)	1 (25.0)	0	5 (8.9)
Study medication non-compliance	0	0	1 (25.0)	0	1 (1.8)
Lost to follow-up	0	0	1 (25.0)	0	1 (1.8)

N = number of subjects with data, n = number of subjects with that observation
[a] Discharge to ambulatory setting

The majority of the subjects were male (44 subjects, 78.6%). Mean (SD) age was 37.0 (10.65) years. At baseline, mean (SD) weight was 78.1 (16.93) kg, height was 175.2 (8.28) cm and BMI was 25.39 (5.367) kg/m². The median (range) duration at baseline since the first onset of psychotic symptoms and since the first antipsychotic treatment was each 3.0 (1-39) years. The majority of subjects (41 subjects, 73.2%) had been hospitalized before.

The majority of subjects in this study (35 subjects, 62.5%) used a daily dose of 6 mg paliperidone ER. Fifteen subjects (26.8%) took a daily dose of 9 mg paliperidone ER. Two subjects had a paliperidone ER dose increase from 6 to 9 mg/day. Reasons for this dose increase were insufficient efficacy (1 subject) and not finding the 9-mg tablets at study entry (1 subject). Four subjects were not compliant with study medication intake (6 mg paliperidone ER) until completion of treatment or premature discontinuation and switched between paliperidone ER doses of 0 and 6 mg once daily.

EFFICACY RESULTS:

Primary Efficacy Analysis

The primary efficacy parameter of this study was the number of subjects with at least 40% improvement in total PANSS-EC from baseline to endpoint. In total, 25 subjects (44.6%) had at least 40% improvement in total PANSS-EC score from baseline to endpoint after treatment with paliperidone ER 6 or 9 mg once daily. The lower and upper limits of the 95% confidence interval (CI) were 31.6% and 57.7%, respectively.

Secondary Efficacy Analysis

The total PANSS-EC scores showed consistent improvement of symptoms over the study period, indicated by a decrease in total PANSS-EC score from baseline. The mean (SD) decrease from baseline in total PANSS-EC score was the largest on Day 5 (-8.7 [5.12]). The PANSS-EC subscale scores excitement, hostility, tension, uncooperativeness, and poor impulse control decreased (improved) consistently over the study period. No obvious differences between subscales were observed in the changes from baseline to endpoint (Day 6).

The mean GAF scores increased over the study period with a mean (SD) increase in GAF score of 11.7 (10.93) from baseline to endpoint, indicating overall improvement of the patients' psychological, social and occupational functioning.

The mean BARS scores decreased over the study period with a mean (SD) decrease from baseline to endpoint in BARS score of -0.7 (0.77), indicating less agitation.

The recordings of verbal aggression incidents using the OAS scale decreased from 14 subjects (25.0%) at baseline to 4 subjects (7.1%) at endpoint. Intervention incidents decreased from 15 subjects (26.8%) at baseline to 4 subjects (7.1%) at endpoint. Physical aggression incidents were rare and reported in at most 2 subjects at any visit, except physical aggression incidents against objects which were reported in 4 subjects (7.1%) at baseline.

The proportion of subjects using lorazepam remained approximately constant during the study period (range: 52.2% - 60.9%) and decreased at endpoint (13.3%).

At endpoint, approximately half of the subjects were diagnosed with schizophrenia (27 subjects, 49.1%). The remainder was diagnosed with psychotic disorder NOS (12 subjects, 21.8%), brief psychotic disorder (9 subjects, 16.4%), schizoaffective disorder (5 subjects, 9.1%), and mood disorder with psychotic features (2 subjects, 3.6%).

Primary Efficacy Parameter: Total PANSS-EC
(R076477SCH3038 Study: ITT Analysis Set for Efficacy)

	Treatment Paliperidone ER				
	Paliperidone ER 6 mg only	Paliperidone ER 9 mg only	Paliperidone ER switch 0 to 6 mg	Paliperidone ER switch 6 to 9 mg	Total
Primary Efficacy Parameter					
Subjects with ≥ 40% improvement in total PANSS-EC from baseline to endpoint (Day 6)					
N	35	15	4	2	56
n (%)	17 (48.57)	5 (33.33)	2 (50.00)	1 (50.00)	25 (44.64)
95% CI	32.01, 65.13	9.48, 57.19	1.00, 99.00	-19.30, 119.30	31.62, 57.66
Secondary Efficacy Parameter: PANNS-EC change from baseline to endpoint					
Total PANSS-EC at baseline					
N	35	15	4	2	56
Mean (SD)	25.2 (2.87)	26.5 (2.77)	24.3 (3.95)	26.5 (2.12)	25.6 (2.91)
Median	25.0	27.0	23.5	26.5	26.0
Range	20; 30	20; 31	21; 29	25; 28	20; 31
Total PANSS-EC at Day 6					
N	34	15	3	2	54
Mean (SD)	17.5 (6.65)	19.5 (5.79)	15.0 (3.61)	12.5 (7.78)	17.8 (6.36)
Median	18.0	18.0	16.0	12.5	18.0
Range	5; 31	9; 30	11; 18	7; 18	5; 31
Change from baseline at Day 6					
N	34	15	3	2	54
Mean (SD)	-7.9 (5.80)	-7.0 (6.39)	-8.7 (5.13)	-14.0 (9.90)	-7.9 (6.02)
Median	-7.5	-8.0	-10.0	-14.0	-8.0
Range	-19; 5	-16; 10	-13; -3	-21; -7	-21; 10

N = number of subjects with data, n = number of subjects with that observation

SAFETY RESULTS:

Adverse Events

A summary of the treatment-emergent AEs (TEAEs) during the study period is presented in the table below.

Summary of Treatment-Emergent Adverse Events
(R076477SCH3038 Study: Safety Population)

	Treatment Paliperidone ER				Total
Subjects (n [%]) with	Paliperidone ER 6 mg only N = 35	Paliperidone ER 9 mg only N = 15	Paliperidone ER switch 0 to 6 mg N = 4	Paliperidone ER switch 6 to 9 mg N = 2	N = 56
Any TEAE	5 (14.3)	1 (6.7)	2 (50.0)	1 (50.0)	9 (16.1)
Any SAE	1 (2.9)	1 (6.7)	0	0	2 (3.6)
Any mild TEAE	3 (8.6)	1 (6.7)	2 (50.0)	1 (50.0)	7 (12.5)
Any moderate TEAE	1 (2.9)	0	0	0	1 (1.8)
Any severe TEAE	1 (2.9)	1 (6.7)	0	0	2 (3.6)
Any TEAE for which paliperidone ER was permanently stopped	0	0	0	0	0
Any TEAE for which paliperidone ER was temporarily stopped	0	0	0	0	0
Any TEAE at least possibly related to paliperidone ER	2 (5.7)	0	0	0	2 (3.6)

N = number of subjects with data; n = number of subjects with one or more event.

No deaths or AEs leading to discontinuation of paliperidone ER treatment were reported in this study. Treatment-emergent serious AEs (SAEs) were reported in 2 subjects (3.6%): schizophrenia and psychotic disorder.

Overall, 9 subjects (16.1%) had at least one TEAE during the study. All TEAEs occurred in at most 1 subject during the study, except nausea which occurred in 3 subjects (5.4%). Treatment-emergent AEs are presented in the table below.

The majority of TEAEs were mild in severity. Moderate TEAEs were reported in 1 subject (1.8%) and severe TEAEs in 2 subjects (3.6%).

Most TEAEs were considered not or doubtfully related to paliperidone ER by the investigator. No TEAEs were considered very likely related to paliperidone ER by the investigator. TEAEs considered at least possibly related to paliperidone ER by the investigator were reported in 2 subjects (3.6%) during the study (electrocardiogram [ECG] QT prolonged and somnolence each reported in 1 subject).

Incidence of Treatment-Emergent Adverse Events During the Study by System Organ Class and Preferred Term (Regardless Severity and Drug Relatedness)
(R076477SCH3038 Study: Safety Population)

	Treatment Paliperidone ER				Total
System Organ Class, Preferred term, n (%)	Paliperidone ER 6 mg only N = 35	Paliperidone ER 9 mg only N = 15	Paliperidone ER switch 0 to 6 mg N = 4	Paliperidone ER switch 6 to 9 mg N = 2	N = 56
Subjects with at least one TEAE	*5 (14.3)*	*1 (6.7)*	*2 (50.0)*	*1 (50.0)*	*9 (16.1)*
Gastrointestinal Disorders	2 (5.7)	1 (6.7)	0	1 (50.0)	4 (7.1)
Nausea	2 (5.7)	0	0	1 (50.0)	3 (5.4)
Dyspepsia	0	1 (6.7)	0	0	1 (1.8)
Vomiting	0	0	0	1 (50.0)	1 (1.8)
Psychiatric Disorders	1 (2.9)	1 (6.7)	1 (25.0)	0	3 (5.4)
Insomnia	0	0	1 (25.0)	0	1 (1.8)
Psychotic disorder	0	1 (6.7)	0	0	1 (1.8)
Schizophrenia	1 (2.9)	0	0	0	1 (1.8)
Nervous System Disorders	1 (2.9)	0	1 (25.0)	0	2 (3.6)
Headache	0	0	1 (25.0)	0	1 (1.8)
Somnolence	1 (2.9)	0	0	0	1 (1.8)
General Disorders and Administration Site Conditions	1 (2.9)	0	0	0	1 (1.8)
Gait disturbance	1 (2.9)	0	0	0	1 (1.8)
Malaise	1 (2.9)	0	0	0	1 (1.8)
Investigations	1 (2.9)	0	0	0	1 (1.8)
ECG QT prolonged	1 (2.9)	0	0	0	1 (1.8)
Metabolism and Nutrition Disorders	1 (2.9)	0	0	0	1 (1.8)
Hyponatremia	1 (2.9)	0	0	0	1 (1.8)
Skin and Subcutaneous Tissue Disorders	1 (2.9)	0	0	0	1 (1.8)
Rash	1 (2.9)	0	0	0	1 (1.8)

N = number of subjects with data; n = number of subjects with one or more event

Vital Signs

Mean changes from baseline to endpoint in vital signs parameters (pulse rate, SBP and DBP) were generally small, and none of the changes were considered clinically relevant. No vital signs-related TEAEs were reported during the course of the study.

STUDY LIMITATIONS: The study was open-label and no comparator was used.

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